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Role of Monocytes in Heart Failure and Atrial Fibrillation

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Heart failure (HF) is a culmination of pathological processes presenting with debilitating symptoms that highlight a complex interplay between immunological, hormonal, and metabolic systems resulting in impaired cardiac function. HF has a major impact on the quality of life and longevity of the affected patients.[1] Inflammation has been shown to play a pivotal role in the pathogenesis of HF within animal studies, but there has been limited translation of these findings into human research.[2,3]

Monocytes and monocyte-derived macrophages play a role in the development of HF. In human immunology, monocytes undertake phagocytosis to provide protection from foreign pathogens such as bacteria and viruses. Nevertheless, there are distinct subsets of monocytes with potential for beneficial or detrimental effects on HF pathogenesis, although intimate details of the involved processes are not yet fully determined.[4,5] Of importance is the fact that the role of monocytes in cardiovascular diseases is complex and includes inflammation, which subsequently contributes to processes of regeneration, repair, and modulation of the prothrombotic state.[6,7] All these functions are highly relevant to patients with HF, who show progressive impairment of cardiac function and frequently develop atrial fibrillation (AF), an arrhythmia with a high risk of thrombotic complications.

Therefore, of equal interest is the role of the immune system in AF, a very common arrhythmia in HF, which has been strongly linked to inflammation.[8] Atrial and ventricular fibrosis have been documented in patients with AF, with monocytes playing a role in these processes, based on animal studies.[9,10] Indeed, inflammation in the myocardium clearly predisposes to cardiac fibrosis.[11]

Why is this important? Cardiac fibrosis is an active process that is part of the remodeling of the myocardium in response to mechanical, chemical, and electrical stressors, along with the inflammation.[12] Myocardial fibrosis reduces left ventricular (LV) compliance and increases filling pressures and atrial load. This, in turn, promotes LV and atrial fibrosis, predisposing to AF and thus completing the vicious circle.[13] HF and AF should therefore not necessarily be considered as pathophysiologically unrelated entities, and indeed the pathological/inflammatory processes underpinning both conditions seem to overlap and this may, in turn, guide therapeutic options.

The aim of this review article is to identify the role of monocytes and their associated inflammatory cells in the pathogenesis of cardiac fibrosis. Particular focus is given to monocyte subsets and their associated immune response cells in the inflammation process of HF and AF. Considerations on possible therapeutic targets related to these cells in the treatment of HF are also discussed.

Etiology and Pathogenesis of HF

A wide range of cardiac conditions, inherited defects, and systemic disorders contribute to the pathogenesis of HF. Ischemic heart disease is a major cause of HF attributed to chronic ischemia (atherosclerosis/coronary calcification) and acute myocardial necrosis (atherothrombosis).[14] Hypertensive cardiac disease leads to the mechanical myocardial stress and neurohormonal changes that are detrimental to cardiac myocytes. Definitive studies have not only found significant lifetime risk of HF in people with blood pressure of over 160/90, but also provided evidence of improved blood pressure control contributing to reduced incidence of HF.[15,16] Valvular heart disease plays a lesser role as a cause of HF in the developed world attributed to improved living conditions and medical and surgical therapy. Globally, however, rheumatic heart disease is still a major cause for HF.[17]

LV dysfunction secondary to myocardial infarction (MI) is the most studied HF etiology. Cardiac remodeling post-MI includes

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stretching of cardiac myocytes attributed to the raised intraventricular pressures found in acute cardiac ischemia.[18] The noninfarcted myocardium attempts to compensate for the area of myocardial loss. Remodeling of the unaffected myocardium is a consequence of the expanding myocardial collagen scar, as well as the response to neuroendocrine stimuli and increased wall stress.[18]

MI is accompanied by an inflammatory process, involving the migration of macrophages, monocytes, and neutrophils into the necrotic and ischemic areas. The subsequent signaling cascade and neurohormonal activation is responsible for the recruitment of inflammatory cells to site of tissue injury.[19]

The early phase of postinfarct remodeling (within 72 hours) predominantly involves the infarct zone itself and can be associated with the zone expansion. Late remodeling involves the left ventricle globally and is associated with dilatation, changes in ventricular morphology, and hypertrophy. Adverse remodeling leads to cardiac failure attributed to inability to prevent or reverse progressive ventricular dilatation, expansion of the myocardial scar, and deterioration in contractile function.[20]

The role of monocytes/macrophages in postinfarct remodeling has been demonstrated in numerous studies.[19,21,22] There exists a fine balance between excessive and prolonged infiltration of inflammatory macrophages into the infarct myocardium, causing a detrimental inflammatory response with subsequent cardiac fibrosis, dysfunction, and adverse ventricular remodeling.[23,24] In contrast, monocytes/macrophages are also essential to wound healing and tissue repair through phagocytosis, angiogenesis, and favorable remodeling of the extracellular matrix in the infarcted area.[4] It remains unclear how the balance of contrasting roles of monocyte/macrophages is achieved. However, the role of monocyte subset populations may be a logical explanation for the diversity in function.

The hypothesis of monocyte subset heterogeneity and function in MI is formed on the basis of their role in modulating chemokine expression in mice, which, in turn, recruit Ly-6C^{high} and Ly-6C^{low} monocyte subset through C-C chemokine receptor type 2 (CCR2) and C-X3-C motif chemokine receptor (CX3CR) 1, respectively. Ly-6C^{high} monocytes dominate early and exhibit a proinflammatory function. Ly-6C^{low} monocytes dominate later. Ly-6C^{low} monocytes promote myocardial healing through myofibroblast accumulation, angiogenesis, and collagen deposition.[4]

Therefore, targeted therapy toward monocyte subsets is an attractive therapeutic option to facilitate favorable cardiac remodeling. The existence of monocyte/macrophage subset heterogeneity and their step-wise contribution to cardiac remodeling provides an opportunity for specific target intervention in the future.

What Do Monocytes Do?

Monocytes are a type of white blood cell present in the peripheral circulation. The primary roles of monocytes are in the participation of innate immunity and to maintain or replenish different types of macrophages and dendritic cells, which aid in phagocytosis of pathogens.[25] Monocytes make up to 8% of the peripheral blood white cells and play a central role in the host response to exogenous and endogenous pathogen species, such as bacteria and viruses. Additionally, they modulate the inflammatory processes, producing both pro- and anti-inflammatory cytokines and developing macrophages with pro- and anti-inflammatory phenotype.[26]

Monocytes are derived from macrophage dendritic cell precursors that originate from the bone marrow under normal homeostatic conditions. Common myeloid progenitor cells, derived from the bone marrow, are responsible for differentiation of precursor progenitor cells into monocytes.[26] Macrophage dendritic cell precursors mature to form either dendritic cells or macrophages. This process is dependent upon stimulation by cytokines and/or microbial molecules.[27] Evidence to date suggests that both monocytes and dendritic cells diverge at a very early multipotent progenitor stage.[26] Common myeloid progenitor cells give rise to the granulocyte-macrophage lineage, which, in turn, give rise to macrophage dendritic cell precursors and subsequently, the committed monocyte precursor.[28] Control of monocyte/macrophage differentiation is guided by a multitude of transcription factors, the complexity of which is beyond the scope of this review article.[29]

In the 1970s, studies highlighted the increase in monocyte proliferation within the bone marrow in response to inflammatory stimuli, allowing for monocytosis.[30] During steady state, circulating monocytes have a half-life of $\approx$3 days.[31] Monocytes are mobilized from the bone marrow at times of tissue injury and differentiate into macrophages or dendritic cells while mounting an immune response. However, they are also implicated in diseases with proinflammatory shift such as heart failure and atherosclerosis.[32,33] Multiple animal studies have shown a diverse and complex function of monocytes depending upon the inflammatory environment, central to which is the ability of monocytes to be mobilized to site of injury.[34]

With regard to atherosclerosis, monocyte-derived "foam cell" macrophages act as a substrate and thus facilitate the progress to MI. Monocyte counts are further highly increased in other forms of acute cardiovascular pathology.[2,33,35]

Overall, monocytes have been used as indicators of prognosis in humans, with their high numbers being associated with increased risk of recurrent MI, hospitalization, and cardiac death. Available data indicate that monocyte mobilization in acute cardiac disease does not simply reflect response to cardiac damage, but its active involvement in the pathological process.[5,36]

Human Monocyte Heterogeneity

Monocyte subsets were first isolated in 1988 using flow cytometry.[37] Expression of CD14 (lipopolysaccharide receptor) and CD16 (Fc receptor) is used to define human monocyte subsets. It should be noted that changes in expression of monocyte subsets are limited to cell-surface protein expression assessed by flow cytometry, with changes in gene expression being up- or downregulated dependent on functional properties.[38]

Human monocyte subsets do not follow their mouse counterparts, in which initial studies in this field were undertaken. As such, nomenclature for human and mouse monocytes is not directly interchangeable and thus should not be directly compared. Human monocytes do not express Ly6C and description of their subsets is primarily based on expression of CD14 (lipopolysaccharide receptor) and CD16 (FC gamma III receptor; Table 1).[39–51]

Human monocytes are dominated by "classical" $CD14^{++}CD16^{-}$ (Mon1) monocytes (ie, 85%). Humans have at least 2 types of nonclassical monocytes. The CD14++CD16+ (Mon2) subset makes up around 6% of monocytes in humans. CD14+CD16++ (Mon3) human monocytes make up 9% of all monocytes.[4,52] There are many significant differences between Mon2 and Mon3, and, overall Mon2 is phenotypically and functionally closer to Mon1 than to Mon3 (discussed in more detail below). Earlier studies analyzed these 2 subsets together, and such data need to be interpreted with care.

A consensus opinion on the nomenclature of human monocytes in 2010 classed monocyte subsets as classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and nonclassical ($CD14^{+}CD16^{++}$).[53] However, to avoid ambiguity the phenotypic definition and numerical designation (ie, Mon1, Mon2, and Mon3) have been incorporated into the most recent consensus document on monocytes subsets.[54]

Although direct correlation between human monocyte subsets is difficult, their differentiation and role in innate immunity are comparable. In fact, both Mon2 and Mon3 have reduced phagocytic activity, reduced production of reactive oxygen species along with lower levels of CCR2 expression.[55] Several studies have highlighted the presence of raised levels of Mon2 in human inflammatory diseases.[56]

Mon1 is characterized by high expression of CD14, interleukin (IL)-6 receptor, CD64, CCR2, and CD163, with less-dense expression of vascular cell adhesion molecule and CD204. Intracellular adhesion molecule receptor, C-X-C chemokine receptor type 4, CD163, and vascular endothelial growth factor receptor 1 have the highest expression on Mon2. Mon3 has maximal expression of CD16, vascular cell adhesion molecule 1 receptor, and CD204, with much lower expression of CD14, IL-6 receptor, CD64, CCR2, and CD163 that Mon2[57] (Table 2).[42,55,58–87]

Monocyte subpopulations differ in the range of cytokines they can produce in response to stimulation. Mon1 has been shown to preferentially express cytokines IL-1β, IL-6, monocyte chemoattractant protein 1 (MCP-1), an inhibitor of nuclear factor kappa β kinase, whereas Mon2 produces anti-inflammatory IL-10. Interestingly, Mon3 stimulates cytokine production in response to viral rather than bacterial load, further emphasizing the functional differences between monocyte subsets.[40] However, recent experiments showed specific release of IL-6 and IL-8 cytokines by Mon2 and Mon3 in response to bacterial endotoxemia[88] (Table 3).[79,89–94]

Mouse Monocyte Heterogeneity

Distinct mouse monocyte subsets were initially distinguished based on the differential expression of a chemokine receptor, CCR2 (receptor to MCP-1). $CCR2^{+}$ monocytes showed a higher migratory and infiltratory capacity compared with $CCR2^{-}$ cells, most recently being studied in postinfarct cardiac remodeling.[42,95,96] Differential expression of an inflammatory monocyte marker, Ly6C, allowed for better mouse subset characterization.[97] Analysis of the 2 principle mouse monocyte subsets ($Ly6C^{+}$ and $Ly6C^{-}$) is commonly used in experimental research; there is accumulating evidence for the existence of a subset with intermediate phenotype, which resemble human "intermediate" Mon2 subset.[66,76] The subsets differ in expression of surface markers, for example: CD11b and CD115 have a high density of CCR2 and only small numbers of CX3CR1 are present on $Ly6C^{+}$ monocytes. In contrast, $Ly6C^{-}$ monocytes virtually lack CCR2, but express high levels of CX3CR1.[97]

$Ly\text{-}6C^{+}$ monocytes have phagocytic and proinflammatory characteristics. In acute MI, they accumulate promptly in areas of myocardial injury, along with macrophages providing a proinflammatory environment.[98,99] $Ly\text{-}6C^{-}$ monocytes, on the other hand, have been found to have anti-inflammatory properties and this subset promotes post-MI myocardial healing through the processes of myoblast activation, angiogenesis, and collagen formation.[66,100,101] Overall, the $Ly\text{-}6C^{+}$ subset is associated with detrimental effects to myocardium and their high levels in the acute phase of MI delay myocardial healing.[102]

Functional studies have demonstrated that $Ly6C^{+}$ cells release reactive oxygen species, nitric oxide, and inflammatory cytokines (eg, tumor necrosis factor α [TNFα], IL-1β) in response to bacterial infection.[27] The subset migration is potentiated through the CCR2 receptor that initiates a change in the ligand for vascular cell adhesion molecule 1 (VLA 4). Studies have found that $Ly6C^{+}$ monocytes preferentially migrate into the sites of vascular inflammation and CCR2 is central to this process, also promoting the subset maturation toward M1 macrophage phenotype.[96,103]

In the absence of inflammation, $Ly6C^{+}$ transforms into $Ly6C^{-}$, which predominates in the circulation, binding to

Table 1. Phenotypic and Functional Differences Between Monocyte Subsets

	Human (Mon1)	Mouse (Mon1)	Human (Mon2)	Mouse (Mon2)	Human (Mon3)	Mouse (Mon3)
Proportion of total monocytes, %[39,40]	85	40 to 45	5	5 to 32	10	26 to 50
Functional properties[39–41]	High phagocytic activity	High phagocytic activity, proinflammatory	High phagocytic activity. T- cell proliferation and stimulation, angiogenesis, superior ROS production	High phagocytic activity, proinflammatory	Low phagocytic activity, high "patrolling" activity (in vivo), T-cell proliferation and stimulation	Low phagocytic activity, patrolling function, tissue repair
Surface markers present[39,42–44]	CD62L, CCR2, CLEC4D, CLEC5A, IL13Rα1, CXCR1, CXCR2	CCR2, CD11b, CD115, CCR5	CCR2, CD74, HLA-DR, Tie-2, ENG	CCR2, CD11b, CD115	Siglec10, CD43, SLAN	CX3CR1, CD11b, CD115, CCR5
Surface markers absent[39,41,45]	CX3CR1, CD123, p2rx1, Siglec10	CX3CR1 (low)	CD62L, CXCR1, CXCR2, CLEC4D IL13Rα1	CX3CR1 (low)	CCR5, CD62L, CXCR1, CXCR2, CD163, CLEC4D, IL13Rα1	CCR2 (low)
Response to LPS[39,42,46–48]	IL-10, G-CSF, CCL2, RANTES, IL-6, IL-8	ROS, TNFα, nitric oxide, IL-1β, IL10 (low levels), IFN-1, VLA-4, IL-6, CD62L	IL-6, IL-8	ROS, TNFα, nitric oxide, IL-1β, IL10 (low levels), IFN-1, VLA-4, IL-6, CCR7, CCR8	TNFα, IL-1β, IL-6, IL-8	IL-10 (high levels)
Increased gene expression[28,39,42,49–51]	Wound healing and anticoagulation, S-100 proteins, scavenger receptors, C-type lectin receptors, antiapoptosis, response to stimuli (CCR2, THBS1, CD163, RNASE4, EDG3, S100A12, CLEC4D, VEGFA, F5, RNASE2, RNASE6, F13A1, CRISPLD2, PLA2G7CES1, EREG, QPCT)	CD177, FN1, Sell, Mmp8, F13a1, Atrnl1, Ly-6c, Chi313	MHC Class II, presentation and processing (CD14, CSPG2, SLC2A3, CD9, CD163, PLA2G7, MCEMP1, CLEC10A, EVA1, RNASE2, GFRA2, ALDH1A1, GALS2, MARCO, ALOX5AP, S100A12, QPCT, FOLR3, OSM, EGR1, CYP27A1, OLFM1, PAD14, HLADOA, ANG, H19, SCD, calgranulin B, S100A9DDIT4	Inconclusive data	Cytoskeletal arrangement, complement components, proapoptosis, downregulation of transcription (FMNL2, CDKN1C, FCGR3A/B)	Vegfc, G0s2, Ikzf3, Tgfbr3, Cd83, Eno3, Tgm2, Itgax, CD36, Dusp16, Slc12a2, Fabp4

vascular endothelium using CX3CR1 receptors.[51] In response to bacterial infection, Ly6C$^-$ cells release anti-inflammatory cytokines (namely, IL-10). The response to inflammation triggers the differentiation of monocytes into M2 macrophages, which, in turn, release anti-inflammatory cytokines central to tissue repair.[97,104,105]

Release of Monocyte Subsets From the Bone Marrow and Spleen

All 3 subsets are present in the bone marrow.[25,66] After maturation, Mon1 leaves the bone marrow, entering the peripheral circulation through CCR2 chemokine receptors.[59] Previous studies had suggested the ability of Mon1 to differentiate further into Mon2 upon migration from the bone marrow, which enter the circulation.[59] Most recent studies have shown the initial release of Mon1 in response to endotoxemia with the subsequent differentiation into Mon2 and Mon3 subsets.[106] However, analysis of bone marrow samples indicates that cells with Mon2 phenotype are already present in human bone marrow.[107] In fact, cells with the Mon2 phenotype were the dominant monocytic cells within the bone marrow.[57]

Monocyte numbers have been found to follow a circadian rhythm controlled by Arnt-1, which is a key gene in regulating the molecular circadian clock.[108] In contrast to the presence

Table 2. Differential Expression of Surface Markers Between Monocyte Subset

	Human	Mouse
Mon1		
Proportion of total monocytes, %[39]	85[39]	40 to 45[39]
Functional properties[39]	High phagocytic activity[39]	High phagocytic activity, proinflammatory[39]
Surface markers/receptors present		
CD14[49,58]	High	High
CD16[49,58]	Low	Low
CCR2[59–61]	High (increased 26-fold)	High
CX3CR1[49,55,59,60]	Low	Low
CXCR1[49,55,62]	High (increased 5-fold)	Low
CXCR2[49,62]	High (increased 7-fold)	–
CD11b[49,61,63–65]	Low	High
CD115[49,66]	–	High
CD62L[49,58,65]	High (increased 3-fold)	High
CLEC4D[49,67]	High (increased 4-fold)	–
CLEC5A[42,49,67]	High (increased 3-fold)	–
IL13Rα1[49]	High (increased 9-fold)	–
CD54[49,68]	Low (decreased 2-fold)	–
CD40[49,65]	High (increased 6-fold)	–
CD36[42,49,69]	High (increased 2-fold)	–
CD99[49,70]	High (increased 2-fold)	–
CCR1[49,71]	High (increased 2-fold)	–
P2XR1[49]	Low (4-fold)	–
HLA-ABC[49,72]	Low (decreased 1-fold)	–
CLEC10A[49]	Low (decreased 6-fold)	–
GFRA2[49]	Low (decreased 6-fold)	–
HLA-DR[42,49,72,73]	Low (decreased 8-fold)	–
CD163[49,74,75]	Low (decreased 1-fold)	–
CD115[45,49,76]	Low (decreased 1-fold)	High
SLAN[49,77,78]	High (increased 2-fold)	–
CD1d[49]	High (increased 1-fold)	–
CCR5[49,79,80]	Low (decreased 1-fold)	–
CD294[49]	Low (decreased 1-fold)	–
Siglec10[49,81,82]	Low (decreased 7-fold)	–
Mon2		
Proportion of total monocytes, %	5[39]	5 to 32[39]
Functional properties	High phagocytic activity, T-cell proliferation and stimulation, angiogenesis, superior ROS production[39]	High phagocytic activity, proinflammatory[39]
Surface markers/receptors present		
CD14[42,49,58]	High	High
CD16[42,49,58]	Low	Low

Continued

Table 2. Continued

	Human	Mouse
CCR2[49,60,83]	High (increased 8-fold)	High
CX3CR1[49,55,60]	Low	Low
CXCR1[49,55,62]	High (increased 4-fold)	Low
CXCR2[46,49,62]	High (increased 3-fold)	–
CD11b[49,61,65]	High	High
CD115[42,45,49]	Low	High
CD62L[49,65,72]	High (increased 1.3-fold)	–
CLEC4D[49]	High (increased 18-fold)	–
CLEC5A[42,49]	High (increased 5-fold)	–
IL13Rα1[49]	High (increased 2-fold)	–
CD54[49,68]	High (increased 1-fold)	–
CD40[49,65]	High (increased 1-fold)	–
CD36[49,69]	High (increased 5-fold)	–
CD99[49,70]	High (increased 5-fold)	–
P2XR1[49]	Low (decreased 5-fold)	–
HLA-ABC[49,72]	High (increased 1-fold)	–
CLEC10A[49]	High (increased 4-fold)	–
GFRA2[49]	High (increased 3-fold)	–
HLA-DR[49,72,73]	High (increased 2-fold)	–
CD163[49,75]	High (increased 6-fold)	–
SLAN[49,77,78]	Low (decreased 3-fold)	–
CD1d[49]	Low (decreased 5-fold)	–
CCR5[49,79,80]	High (increased 7-fold)	–
CD294[49]	Low (decreased 3-fold)	–
Siglec10[49,81,82]	Low (decreased 21-fold)	–
Mon3		
Proportion of total monocytes, %	10[39]	26 to 50[39]
Functional properties	Low phagocytic activity, high "patrolling" activity (in vivo), T-cell proliferation and stimulation[39]	Low phagocytic activity, patrolling function, tissue repair[39]
Surface markers/receptors present		
CD14[49,58]	Low	Low
CD16[49,58]	High	High
CCR2[49,60,61]	Low	Low/–
CX3CR1[45,49,60,65]	High	High
CD11b[49,61,84]	High	High
CD62L[58,65,85]	Low	Low
P2XR1[49]	High (increased 1.2-fold)	–
HLA-ABC[49,72]	Low (–)	–
CLEC10A[49]	Low (–)	–
GFRA2[49]	Low (–)	–
HLA-DR[49,72,73]	Low (–)	–

Continued

Table 2. Continued

	Human	Mouse
CD163[49,74,86]	High (increased 7-fold)	–
CD115[45,49,76]	Low (decreased 2-fold)	High
SLAN[49,77,78,87]	Low (decreased 7-fold)	–
CD1d[49]	High (increased 4-fold)	–
CCR5[49,79,80]	High (increased 8-fold)	–
CD294[49]	Low (decreased 2-fold)	–
Siglec10[49,81,82]	Low (decreased 3-fold)	–

(–) indicates evidence lacking or under-reported.

of CCR2 ligands present on monocytes during homeostasis, the release of patrolling monocytes is dependent upon the G-protein-coupled receptor for sphingosine-1-phosphate, the deficiency of which leads to an inability of Mon3 to redistribute from the bone marrow.[109]

Under certain inflammatory conditions (eg, cancer, HF, MI, and stroke), mouse models have shown the spleen to be capable of extramedullary monopoiesis.[110] Release of monocytes from the spleen is dependent upon angiotensin II as opposed to CCR2 in the bone marrow.[63] Furthermore, in cardiovascular disease, there is a dependency upon a separate chemokine, chemokine (C-X-C motif) ligand 1, to direct the release of monocytes from both the splenic and bone marrow reservoirs.[111]

Roles of Circulating Monocyte Subsets

Monocyte studies involving gene analysis highlight the preferential expression of genes involved in angiogenesis, wound healing, and coagulation (namely, Mon3).[49] Alternatively, Mon1 have a higher capability to produce IL-1β and TNFα in response to bacterial lipopolysaccharides.[40] During the inflammatory process, both Mon1 and Mon2 bind to MCP-1, thus allowing monocytes to invade into human tissue and perpetuate the inflammatory cascade.[112]

In contrast, Mon3 bind to CX3CR/chemokine (C-C motif) ligand 3 receptors through the leucocyte functional antigen 1, subsequently stimulating the release of IL-1β and TNFα. Such pathophysiology has been implicated in autoimmune conditions, such as rheumatoid arthritis.[40]

Table 3. Differential Cytokines Production by Monocyte Subsets in Response to LPS in Human and Mouse Models Relative to Mon2

Plasma Cytokine	Mon1	Mon2	Mon3
G-CSF[49,89,90]	High	Low	Low
IL-10[40,49,91,92]	High	Low	Low
CCL2[27,49,93]	High	Low	Low
RANTES[49,79]	High	Low	Low
IL-6[27,49,65,88]	High	Intermediate	Intermediate
IL-8[40,49,88,90]	High	High	High
IL 1-β[27,49,65]	Intermediate	Intermediate	High
TNF-α[49,65,94]	Intermediate	Low	High

CCR2 indicates C-C chemokine receptor type 2; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; LPS, lipopolysaccharide; RANTES, regulated on activation, normal T cell expressed and secreted; TNF-α, tumor necrosis factor alpha.

Role of Monocytes in Cardiovascular Disease and Heart Failure

Inflammation plays a pivotal role in the pathogenesis of HF. Cytokines, such as IL-6 and TNFα, are important markers of active disease and prognosis.[113,114] Compromise of the myocardium has multiple etiologies, ranging from ischemic heart disease, hypertension, cardiac arrhythmias, and metabolic diseases. Neopterin, which is a metabolite of guanosine triphosphate, has been found to be elevated in patients with HF and this is said to be a marker of monocyte activation.[115]

The transmigration of cells to the site of tissue injury relies upon specific cell-surface molecules, namely monocytes and cell adhesion molecules, that respond to signaling by cytokines released from the injured vessel wall.[4] Once inside the vessel wall/myocardium, monocytes will differentiate into macrophages, which promote tissue repair. The complex interactions within injured myocardial cells lead to formation of both pro- and anti-inflammatory cells. In pathological conditions, there is an override of tissue homeostasis and uncontrolled inflammation leads to the exaggerated release of macrophages, which, instead of healing tissue, cause tissue damage with adverse remodeling. Therefore, trying to regulate the monocyte/macrophage balance is a logical therapeutic strategy.

As discussed, under specific stimuli monocytes will differentiate into macrophages. Macrophages play a vital role in the phagocytosis and removal of pathogens.[116] Although

inflammation aims to protect against infection, it can cause damage to the vascular endothelium, activation of tissue macrophage, and activation of cytokine pathway migration of smooth muscle cells to the intima of the arterial wall, thus accelerating the process of atherosclerosis.[117]

Hypoxia and myocardial necrosis drive an inflammatory process in the injured myocardium, which involves activation of monocytes/macrophages. These cells, in turn, are capable of producing cytokines, chemokines, and growth factors.[118] In patients with diabetes mellitus who suffer an ST-elevation MI, Mon2 subsets were elevated and their high counts predict recurrent cardiovascular events and death.[119]

In ischemic HF, Mon1 have similar counts to controls with coronary artery disease without HF, but their numbers are increased during HF decompensation. In contrast, Mon2 is the only subset increased in patients with stable HF and it shows a further sharp increase in acute HF.[119,120] Of interest, high Mon2 counts were associated with better survival in that study, using a combined outcome of death and rehospitalization. This suggests a presence of potentially protective properties of this subset in patients with failing hearts. Analysis of their functional status was not analyzed in the study, and it is difficult to be certain what drives possible benefits or dangers associated with the subset.

There is some controversy on the role of Mon3 in HF given that both their depletion or no change were observed.[119,120] This may be attributed to differences in etiology of the studied patients, for example, an accelerated homing of Mon3 in patients with nonischemic HF, as observed in the study with mixed HF etiology. A notable limitation in some studies is the lack of control for comorbidities that may be responsible for the abnormal release of monocytes. Despite this potential limitation, one should still recognize the importance of monocytes in the inflammatory process that happens in HF with further research in human subjects, particularly focusing on Mon2 being justified.[5]

A compromised myocardium provides multiple stimuli for monocyte recruitment in patients with HF. The presence of excessive LV and atrial stretch in experimental studies of mice with HF with preserved ejection fraction on the background of hypertension has shown to stimulate myocardial resident macrophages to signal the release monocyte chemoattractants (including MCP-1, interleukins).[121] Monocyte recruitment is further amplified by the presence of tissue hypoxia and ischemia[122,123] (Table 4).[124–136]

Excessive monocyte/macrophage cardiac recruitment leads to a vicious circle of myocardial damage and remodeling. This process involves apoptosis of cardiomyocytes.[122,123] It has been shown that monocyte TNFα triggers production of the inducible type of nitric oxide synthase, uncontrolled oxidative stress, and, consequently, apoptosis and tissue necrosis.[122] In the inflammatory process, cytokine release by stimulated monocytes attracts even more monocytes to the compromised myocardium, thus contributing to the vicious circle (Figure 1).

Monocyte Activation in Cardiac Fibrosis

Cardiac fibrosis is the consequence of an activated monocyte/macrophage cascade in HF. Both cellular and extracellular processes are involved in cardiac fibrosis. Within the extracellular matrix, cardiac fibroblasts make up ≈60% of all cells, in fact, outnumbering cardiomyocytes. They are relatively scarce in a healthy adult heart, and a rise in the cell population occurs during a pathological process. This is suggested, for example, by evidence from mice models where tissue injury led to a rise in IL-β production and, consequently,

Table 4. Changes in Mon2 and Mon3 in Cardiovascular Disease States

Condition	Mon2	Mon3
Stable coronary artery disease[33,124,125]	No change vs healthy control	No change vs health control
Acute myocardial infarction[126–128]	2.5-fold increase, positively correlates with troponin T level	No change, no correlation with troponin T level
Unstable angina[129–131]	Increased (in intermediate-high-risk patients' vs low-risk cohort)	No change (no difference with risk severity)
Acute heart failure[5,132,133]	Increased, raised CD41 count relative to mon3	No change
Chronic heart failure[120,134]	Increased expression, correlates with NYHA class/LVEF/NT-proBNP	Increased but no correlation to NYHA class/LVEF/NT-proBNP
Chronic heart failure[135]	No change vs healthy control No association with end-diastolic dimension	Increased percentage vs health controls Inverse relationship with end-diastolic dimension
Abdominal aortic aneurysm[136]	Increased vs healthy controls	Increase count vs healthy controls

LVEF indicates left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

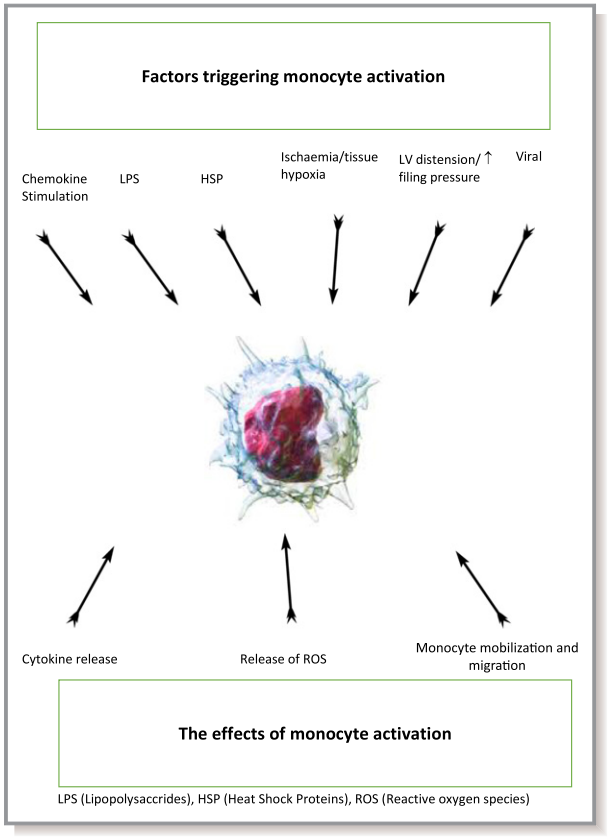

Figure 1. Triggers for monocyte activation and subsequent function. HSP indicates xxx; LPS, lipopolysaccharide; LV, left ventricular; ROS, reactive oxygen species.

to fibroblast expansion.[137] This, in turn, propagates inflammatory cell infiltration and further cytokine production in the site of tissue injury.[137] In such cases, there is an increase in rate of differentiation of precursor cells (eg, monocytes, endothelial progenitors, pericytes, and bone marrow circulating progenitor cells) into fibroblasts.[138,139]

The process by which monocytes can potentiate the cardiac inflammatory response leading to fibrosis is reliant on monocyte cell-surface receptors. One such group of receptors is termed the Toll-like receptors (TLRs), which are members of the pattern recognition system, but also able to respond to endogenic stimuli.[140] Although TLR4 is present on different types of cells, its highest density has been noted on monocytes, reflective of their vital role in innate immunity. In addition, monocyte density of CD14 has also been found to be higher in patients with moderate-severe heart failure in comparison with normal or mild LV impairment.[141,142]

Expression of TLR4 on monocytes is linked to the degree of cardiac injury and remodeling.[143] Evidence thus far points to the enhanced recruitment of TLR4-expressing monocytes into a compromised myocardium in both human and mouse studies.[144,145] The remodeled myocardium has a higher count of $TLR4^{+}$ monocytes compared with a healthy myocardium,[146] thus creating a proinflammatory environment. Indeed, TLR4-deficient mice have a lower inflammatory burden post–acute ischemia and reduced apoptosis of cardiomyocytes.[147]

Further evidence has pointed to several mechanisms by which monocyte activation takes place in HF. With respect to the immune response found in cardiovascular disease, lipopolysaccharides that are found on Gram-negative bacteria act as the ligand component for the activation of monocytes (eg, binding to CD14 and TLR4 as previously mentioned) and triggering cytokine release. This endotoxin-cytokine hypothesis centers on bacterial transition into the circulation through entrance through a permeable bowel membrane.[148] This is promoted by venous congestion developed through HF increasing membrane permeability. The overexpression of inflammatory cytokines amplifies the process leading to a pathological loop often culminating in symptomatic HF.[142]

An alternative mechanism to the introduction of bacteria into the circulation in HF involves activation of the sympathetic system, a common feature of HF.[149] The sympathetic activity is thought to redistribute blood flow away from the splanchnic circulation, which, in turn, leads to transient ischemia in the bowel. This causes an increase in endothelial permeability and entry of the proinflammatory bowel contaminants into the circulation. This mobilizes inflammatory cells from bone marrow (and the spleen depot), and numerous studies have found an increase in blood leucocytes in patients with advanced HF, thus supporting this hypothesis.[150,151]

It is likely that no 1 single hypothesis fully explains the process by which monocytes and their surface receptors are stimulated to propagate cardiac fibrosis. Both systemic and local cascades of inflammatory pathways exist to enhance the stimuli for monocyte-triggered cardiac fibrosis.

Is There a Different Role of Monocytes in HF With Preserved Ejection Fraction?

HF with preserved ejection fraction (HFpEF) is a common condition that constitutes half of all cases of HF. Its diagnosis is based on the presence of a “normal” ejection fraction together with signs and symptoms suggestive of HF and evidence of diastolic dysfunction in the form of prolonged LV relaxation and filling, increased diastolic stiffness, and elevated LV end-diastolic pressures.[152] An aging population, along with multiple comorbidities, predisposes to the increasing rates of HFpEF. Limited advancement has been made in the treatment of these patients. The complexity in the pathogenesis of LV remodeling in HFpEF with insufficient understanding of its mechanisms likely contribute to the limited progress in this field.

HF symptoms in patients with diastolic dysfunction are attributed to reduced stroke volume secondary to increased cardiac stiffness. This reflects changes in the

extracellular matrix with cardiac fibrosis and cardiomyocyte hypertrophy.[153] Majority of such patients have a prolonged history of hypertension with an accelerated accumulation of monocytes in the presence of pressure overload.[154,155] Monocytes have been found to mediate the inflammatory process by releasing chemokines, such MCP-1, TNFα, and transforming growth factor-β (TGF-β), which, in turn, play proinflammatory and -fibrotic roles.[156,157] MCP-1 knockout mice studies have shown significant suppression of fibrosis and macrophage activation.[158] In relation to cytokines, TNFα, IL-1, IL-6, IL-8, and MCP-1 in the peripheral circulation of patients with chronic HF are shown to be elevated.[159–161]

Monocytes are 1 of the major sources of these inflammatory cells. Such cells have been shown to be of prognostic importance in patients developing HFpEF.[162] This is unsurprising given that the comorbidities of patients with HFpEF have long established an inflammatory origin in their etiology, for example, chronic vascular inflammation found in patients with coronary artery disease.

The processes described lead to structural and mechanical remodeling of the heart muscle through the interstitial deposition of extracellular matrix proteins such as collagen.[163] The resulting hypertrophic changes of the myocardium cause the findings of diastolic dysfunction. It is this inflammatory and fibrotic process that underpins the changes observed in patients with diastolic dysfunction and HFpEF.

However, until very recently, all pathophysiological evidence for monocytes in HF were based on HF with reduced ejection fraction. More recently, patients with HFpEF have been found to have raised monocyte counts, specifically the Mon2 subset.[164,165] Data on macrophage/monocyte polarization in human patient cardiac tissue showed increased presence of TGF-β-expressing leucocytes, resembling blood Mon2 subset.[166] In agreement with this, animal studies have shown cardiac upregulation of M2 macrophages, which contribute to cardiac fibrosis in hypertension.[167] Healthy monocytes exposed to serum from HFpEF patients preferentially develop M2 macrophage profibrotic features.[154] In this study, patients with HFpEF had elevated cytokine levels (eg, TNFα, IL-6, and IL-12) and MCP-1, which paralleled high monocyte counts. Furthermore, there was a positive correlation between monocyte numbers and worsening parameters of diastolic dysfunction.[154] An acute ischemic injury is accompanied by conversion from M1 to M2 macrophages, a type of macrophage known to provide a profibrotic inflammatory environment.[168]

Despite the relative scarcity of the data, it is likely that this monocyte/macrophage-driven inflammatory environment is largely responsible for the fibrotic changes in HFpEF. Their increase number causes an increase in collagen deposition and conversion of cardiac fibroblasts to myofibroblasts (Figure 2).

What About Atrial Fibrillation?

Atrial fibrosis is a hallmark of the structural cardiac remodeling that takes place in AF, causing an increase in the frequency of AF paroxysms, which, in turn, increase likelihood of progression to permanent AF.[169] Atrial fibrosis has been observed in biopsies from patients with AF[148] as well as in patients with specific risk factors predisposing to AF, such as valvular heart disease,[170] dilated and hypertrophic cardiomyopathy,[171] and advanced age.[172]

Structural heart remodeling in aging and heart disease is associated with fibrosis. With aging, there is a progressive enlargement of the extracellular compartment in the atrial septum attributed to accumulation of connective tissue fibers.[173] This process is even more prominent in an HF model,[174] where larger areas of fibrosis were observed, similar to the "replacement fibrosis" observed after tissue damage and cell death. Atrial fibrosis may, in itself, be sufficient to increase susceptibility to AF, as shown in mice with atrial fibrosis attributed to overexpression of TGF-β1.[175]

Although there are strong indications from animal models that atrial fibrosis can be proarrhythmic,[8] some questions regarding the role of atrial fibrosis as a substrate of AF are still unresolved. Experimental data linking inflammation and atrial fibrosis have been conflicting. Most recent data point to the upregulation of profibrotic factors, such as TGF-β, and accumulation of collagen in the atrial interstitium.[176] However, previous studies showed preserved interstitium despite changes in atrial architecture and myocyte characteristics.[177] The discrepancy between the data can be partly explained by the findings that profibrotic factors may not accumulate over shorter time periods found in some studies, and that increased gene expression of markers of fibrosis may be the first sign of later fibrosis.[178] Another proinflammatory peptide, TNFα, has been shown to be elevated in patients with chronic AF. Released largely by monocytes and macrophages, TNFα has been found at higher levels in patients with nonvalvular AF than those in sinus rhythm.[179] This correlates with a more-significant leuckocyte infiltration and more-advanced fibrotic changes in the atria.

Some, but not all, human studies have confirmed excessive atrial fibrosis in chronic AF patients compared with those with sinus rhythm.[180,181] The degree of atrial fibrosis and profibrogenic status correlates with the persistence of AF.[182] However, from these studies, it is unclear whether the fibrosis is caused by underlying structural disease leading to AF or by AF itself. Given that the degree of the underlying heart disease is not well documented in every study, it is currently difficult to establish the magnitude of effects of particular conditions to the development of atrial fibrosis in AF patients. Some insights into profibrotic effects of background cardiac pathology versus AF come from a comparison of structural heart disease patients with and without AF.[170] In this study, AF itself has not

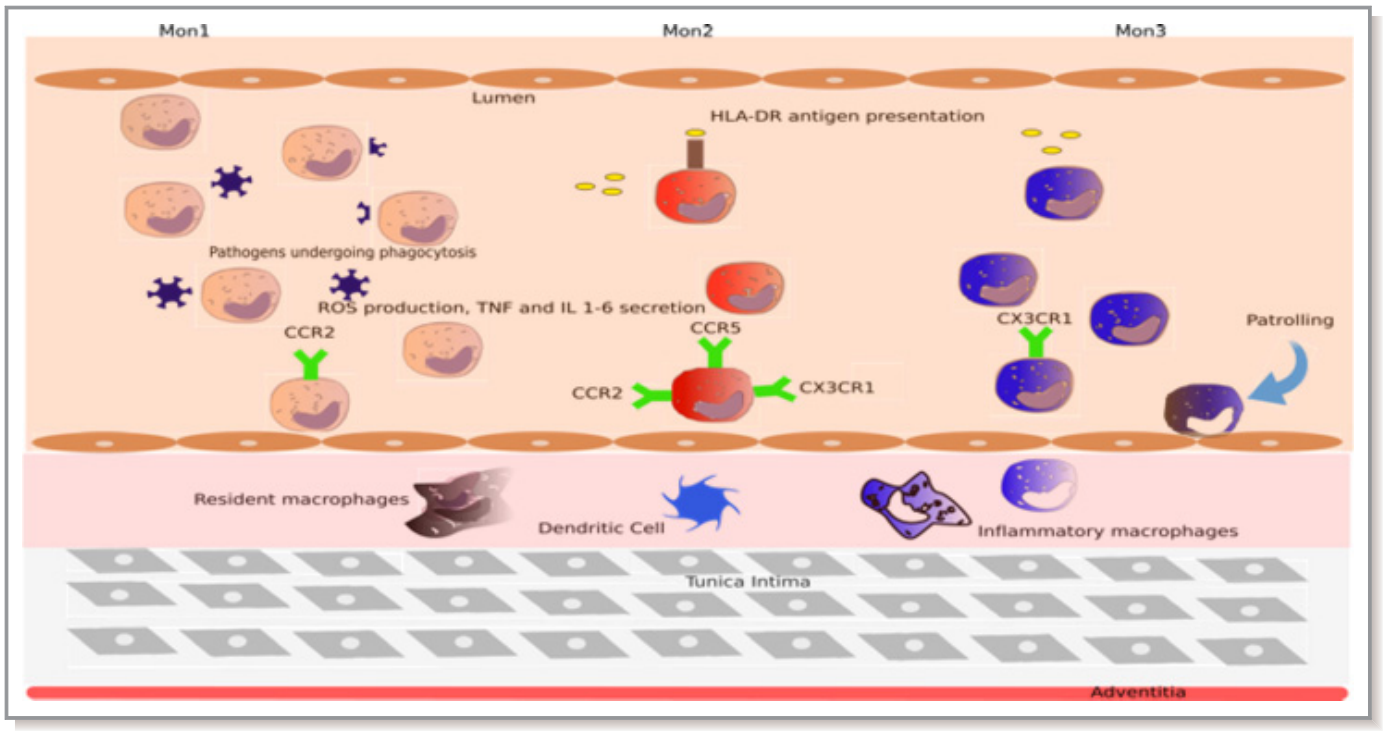

Figure 2. Role of monocyte subsets in heart failure. Human monocytes are classified as Mon1, Mon2, and Mon3, respectively, based on their levels expression of CD14 and CD16. Mon2 are increased in patients with heart failure and are recruited to the myocardium in times of tissue injury, whereas Mon3 serve more of a patrolling function and are not so rapidly recruited. Monocyte subsets then differentiate into dendritic cells and inflammatory macrophages to further potentiate the fibrosis. CCR2/5 indicates C-C chemokine receptor type 2/5; CX3CR1, C-X3-C motif chemokine receptor 1; HLA-DR, human leukocyte antigen – antigen D related; IL, interleukin; ROS, reactive oxygen species; TNF, tumor necrosis factor.

been found to be associated with atrial fibrosis, but is instead related to the severity of the structural heart disease. Given the significant differences in AF pathogenesis among patients with or without structural heart disease, studies dedicated to nonvalvular AF would be essential to shed further light to the interactions between AF and connective tissue deposition in the atria.

The question therefore remains of how important atrial fibrosis is as a causative factor for AF in humans. Most animal models show that atrial dilation is accompanied by both atrial fibrosis and conduction disturbances, although conduction disturbances could also be observed in the absence of atrial fibrosis.[183,184] However, frequently used mice models of AF have significant limitations attributed to the fact that this species has a high physiological heart rate and thus AF induced in mice may not accurately reflect pathological processes in humans. In patients undergoing open heart surgery, degree of fibrosis does correlate with the occurrence of postoperative AF[185] and with the recurrence of AF.[181]

Similar to AF, cardiac fibrosis is related to myocardial inflammation and oxidative stress secondary to infiltration of inflammatory cells, thus suggesting further pathophysiological links between the 2.[186] The oxidative stress observed in these conditions is further amplified by stimulation of the renin angiotensin-aldosterone system, which aids NADH oxidase release.[187] IL-1, IL-6, TNFα, and MCP-1 are all upregulated in AF predisposing to fibrotic changes and the related electrical and structural remodeling, typical of AF. The role of inflammation in AF development is highlighted by the correlation with C-reactive protein (CRP) and has been found, in postoperative patients, to be a surrogate marker for predictor of new-onset AF.[188] Also, postablation CRP levels can be used as a marker for risk of recurrence.[189]

Further evidence on the role of cardiac fibrosis in AF comes from experimental and clinical studies demonstrating that prevention of atrial fibrosis can delay the development of AF. Several treatments (eg, statins, angiotensin-converting enzyme inhibitors, AT_1-receptor blockers, fish oil, and glucocorticoids) have been proven to effectively delay the structural remodeling process and reduce AF burden in a variety of experimental models.[190–195] Several post-hoc analyses of clinical trials and small-scale, proof-of-principle studies indicate utility of such approaches in humans, but improvement of the patients' hemodynamics with normalization of atrial pressures might also have contributed to the beneficial effects of these compounds.[196]

The role of ventricular fibrosis in AF is less established. Patients with AF have more-marked ventricular fibrosis than those with sinus rhythm.[197] Although atrial and ventricular fibrosis are likely to share a common mechanism, there are much more-limited findings of profibrotic gene expression in ventricular fibrosis in comparison with the atrium.[198] TGF-β seems to play a major role in ventricular fibrosis in AF, but further data are needed to establish the mechanisms that trigger its expression in the myocardium and the role of monocytes and macrophages as a source of TGF-β in the heart.[199]

Conclusion

Monocytes represent an essential component of the innate immune system and play a vital role in cardiovascular health. The beneficial effects of monocytes include their contribution to cardiac remodeling in response to physiological and pathological changes in hemodynamics, elimination of pathogens, involvement in apoptosis, and phagocytosis of necrotic tissues. However, excessive inflammatory response to cardiac insult can be harmful to the human body and can lead to cardiac fibrosis and heart failure. There is a fine balance between monocytes that predisposes to beneficial or deleterious effects. Existence of several subsets of monocytes is likely to explain the diversity of the monocyte effects in health and disease. To date, few studies have specifically looked at monocytes subsets and their key characteristics as contributors to cardiac fibrosis and AF.

Monocytes trigger an inflammatory cascade involving the release of cytokines. Such cytokines migrate to the myocardium and adhere to the endothelial wall. Infiltration into the myocardium is a complex process, but 1 that ultimately leads to fibrosis and symptoms of HF. To better identify therapeutic targets, the role of monocytes and their individual subsets, in the pathophysiology of AF and its complications, such as HF, must be determined.

Disclosures

Lip serves as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. Shahid and Shantsila have no conflicts to disclose.

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